

Estimation of Serum Copper, Manganese, Selenium, and Zinc in Hypothyroidism Patients

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Abstract

Decreased thyroid hormone synthesis and low levels of circulating thyroid hormones result in biochemical and/or clinical hypothyroidism. Deficiency of thyroid hormones causes many metabolic processes to slow down. The maintenance of optimal health requires an adequate supply of carbohydrates, proteins and lipids, and macronutrients, micronutrients, and trace elements. In this work, the serum content of the trace elements; Zn, Cu, Mn, and Se in hypothyroidism patients was determined and compared to that of normal subjects. Seventy three hypothyroid patients and fifty normal healthy control persons participated in this study. Serum zinc and copper were determined using flame atomic absorption spectrophotometer, while determination of manganese and selenium were done using flameless atomic absorption spectrophotometer. The results showed that serum zinc and selenium level of hypothyroidism patients are significantly lower ($p < 0.05$) than the level in normal subjects. A significant increase in serum manganese level was demonstrated in patients as compared with that of the normal subjects while there is no significant difference between the groups ($p > 0.05$) in serum copper. The results of this work as discussed indicate, the role of these trace elements in many metabolic process either as essential nutrients or as cofactors for different enzymes contributed directly or indirectly to the hypothyroidism. Consequently, the results of this study suggest that the metabolism of zinc, manganese, and selenium is abnormal in hypothyroidism disease.

Keywords: Hypothyroidism, Copper, Manganese, Selenium, and Zinc.

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Introduction

The maintenance of optimal health requires an adequate supply of carbohydrates, proteins and lipids, and macronutrients, micronutrients, and trace elements (Solomons 1993). Many trace elements play an essential role in a number of biological processes through their action as activators or inhibitors of enzymatic reactions, by competing with other elements and proteins for binding sites, by influencing the permeability of cell membranes, or through other mechanisms. Trace elements are known to influence hormones at levels of action, including hormone secretion and activity and binding to target tissue. Conversely, hormones influence trace metals metabolism at several

levels of action, including excretion and transport of trace metals (Tapiero and Tew 2003; Stefanidou et al. 2006; Aschner 2006; Schomburg and Köhrle 2008). Hence, trace elements assay in biological fluids can be used as diagnostic or prognostic aid in patients with different hormonal disturbances alongside with other biochemical parameters.

Thyroid hormones play an important role in human body metabolism. After binding with a specific nuclear receptor, T3/T4 induces transcription of genetic code via mRNA and regulates proteosynthesis in most tissues. Thyroid hormones regulate the rate of metabolic processes and consequent

development of organism (Kvicala and Zamrazil 2003).

Decreased thyroid hormone synthesis and low levels of circulating thyroid hormones result in biochemical and/or clinical hypothyroidism. This condition occurs more frequently in women; the overall incidences are about 3% of the general population (Standbury and Kroc 2000). Hypothyroidism probably is initiated by autoimmunity against the thyroid gland in addition to different other causes (Wartofsky 1996). The thyroid glands of most of these patients first have autoimmune "Thyroiditis", which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands called thyroid goiter (Meng 1996).

Deficiency of thyroid hormones causes many metabolic processes to slow down. Symptoms of hypothyroidism include enlargement of thyroid gland-or goiter, impairment of cognition slowing of mental and physical performance, increased risk of coronary heart diseases many and different other symptoms (Surks and Ocampo 1996).

The status of different trace elements in hypothyroidism is not well established. Furthermore, serum manganese in hypothyroidism patients is not studied previously. In this work, the serum contents of some trace elements (Zn, Cu, Mn, and Se) was determined in hypothyroidism patients and compared with that of normal subjects.

Material and Methods

Patients

Seventy three hypothyroidism patients, their age range between 19-64 years, 41 females and 32 males, participated in this study. The patients were diagnosed depending on the results of the following examinations: clinical examinations, serum hormones level (T3, T4 and TSH), computed tomography (CT scan),

pathological examination, and fine needle aspiration (If needed).

Normal Controls

Fifty normal healthy persons aged (19-55) years (29 females and 21 males) were used as control.

Samples Collection and Preparation

About five milliliters of venous blood from fasting subjects were drawn by utilizing disposable plastic syringes in the morning and transferred into sterile test tube. The blood was allowed to clot and centrifuged at 4000g for 10 minutes. Sera were separated and stored at -20°C until analysis.

Analysis of Trace Elements

Determination of Zinc and Copper

Serum zinc and copper were determined using flame atomic absorption spectrophotometer (AA-646) (Shimadzu, Japan). Samples were diluted 1:10 with 6% n-butanol solution. This method achieved 30% increase in sensitivity as compared with the use of deionized water only as diluent (Meret and Henkin 1971). This effect is due to decreased viscosity and difference in droplet formation and this technique is widely used (Taylor and Bryant 1981). The level of sera zinc and copper were calculated after application of absorbencies on suitable calibration curve for each element made from standard solutions.

Determination of Manganese and Selenium

Serum samples were diluted with an equal volume of deionized water for estimation of serum Manganese and diluted two fold with deionized water to estimate serum selenium. Flameless atomic absorption spectrophotometer (Perkin-Elmer Model 503) was used to estimate the level of these elements in the diluted sera. Level of sera Manganese & Selenium were calculated after application of absorbencies on suitable calibration curve for each element from standard solutions.

Statistical Analysis

The results of serum element concentrations were expressed as mean±standard deviation. The level of significance was determined by employing pooled t-test. Only when p-value was less than 0.05 was the difference between two groups considered as statistically significant.

Results

Table (1) showed the results of serum trace elements expressed as mean±standard deviation. Serum zinc and selenium level of hypothyroidism patients are significantly lower ($p<0.05$) than the level in normal subjects as shown in Table (2). A significant increase in serum manganese level was demonstrated in patients as compared with that of the normal subjects while there is no significant difference between the groups ($p>0.05$) in serum copper as shown in Table (1).

Table 1. The serum concentration of Trace Elements in Hypothyroidism patients and normal patients expressed as (mean ± standard deviation).

Trace Elements	Normal Control $\mu\text{mol.L}^{-1}$	Hypothyroidism $\mu\text{mol.L}^{-1}$
Copper	21.73±6.44	19.55±7.42
Manganese	0.70±0.37	0.94±0.77
Selenium	1.35±0.44	1.17±0.54
Zinc	9.08±2.48	8.09±2.31

Table 2. Probability values and significance of difference for the comparison between hypothyroidism patients and normal control groups in the serum concentration of the studied trace elements.

Trace Elements	P-value	Significance
Copper	0.067	Non-Significant
Manganese	0.009	Significant
Selenium	0.027	Significant
Zinc	0.020	Significant

Discussion

The significant decrease in the level of Zn in hypothyroidism patients in comparison to that of normal subjects are observed in other different researches (Buchinger et al., 1988; Yoshida et al. 1990; Zhang et al. 2004). One possible explanation for these findings, that gastrointestinal absorption of zinc is severely impaired in hypothyroidism subjects. An alternative explanation would be a change in zinc distribution; the low zinc level may reflect sequestration of zinc by the liver or other tissues (Yoshida et al. 1990). Another explanation is due to the significant influence of TSH in the variation of the concentration of

iodine, selenium and zinc in normal and altered human thyroid tissues (Bellisola, 1998).

In one research, the serum zinc levels in hyperthyroid patients were clearly higher than in the hypothyroid patients group (Aktuna et al. 1993).

Zinc has important roles in thyroid metabolism (Nishi et al., 1980; Fabris, 1994; Dhawan et al., 2007) and a fundamental role in protein synthesis (Freake et al. 2001). It involves in T3 binding to its nuclear receptor, and participates in the formation and mechanism of action of TRH (Pekary et al. 1991). Olivieri et al. (1996) reported in hypothyroidism patients, thyroid hormones did

not correlate with indices of zinc status; although, in rats and humans (Ruz, et al. 1999), zinc deficiency has been led to decrease iodothyronine levels and also they found a strong positive association between zinc and FT3 levels (Olivieri et al. 1996). Hence, the correlation between hypothyroidism and serum zinc is not a simple correlation and needs more specific studies.

The decrease in serum selenium levels in hypothyroidism patients is in agreement with the studies of other researchers indicating the important role of selenium in controlling the thyroid gland functions (Schomburg and Köhrle 2008; Erdal et al. 2008)

Statistically significant correlations were found among indexes of selenium status and indexes of thyroid hormone metabolism and function. Concomitant deficiencies of both key elements for thyroid hormone metabolism are especially dangerous and Se from the point of thyroid hormone regulative functions (Kvicala and Zamrazil, 2003).

In other studies, using animals, selenium deficiency in rats inhibited the production of T3 from T4. It is concluded that, since both T3 production and catabolism are inhibited by selenium deficiency, there is little change in hepatic T3 stores (Beckett et al. 1992). Selenium deficiency in rats is characterized by elevated serum T4 and decreased serum T3 concentrations, and low liver iodothyronine 5'-deiodinase I and brain iodothyronine 5'-deiodinase II activities (Chanoine et al., 1992).

The iodothyronine deiodinases, which are responsible for the conversion of thyroxine (T4) to its active form, triiodothyronine (T3), are selenoenzymes (Arthur 1996; Chanoine 2001). However, another data reported that in hypothyroid patients, a poor Se status was associated with a diminished 5-deiodinase, leading to increase T4 levels and decreased T3/T4 ratios (Beckett and Arthur, 1994; Campos et al. 1997).

Selenium supplementation caused an increase in plasma selenium values (Nève, 1995; Chanoine 2001) but did not affect the activity of the selenoenzyme glutathione

peroxidase used as a marker of selenium status and caused a significant decrease in thyroglobulin values (Chanoine 2001).

In conclusion, when selenium is depleted, there is less Se to form the deiodinase enzymes which convert T4 to T3, resulting in low T3 and hypothyroidism. In addition, there is less selenium to form glutathione peroxidase, one of the body's prime antioxidants. This results in greater levels of reactive oxygen species and hydrogen peroxide, which lead to increased damage to the thyroid gland.

There is no significant change in serum copper in patients with hypothyroidism as compared to that of normal subjects. There is no precise evidence, in literature, corresponding to the correlation between serum copper and hypothyroidism. More investigations are required using larger sample size and severe hypothyroidism to be sure about the lack of correlation between the disease and different copper indexes.

A significant increase in manganese levels of hypothyroidism patients was observed in comparison to that of normal subjects (Tables 1 and 2). Manganese is a cofactor of many important enzymes especially, manganese superoxide dismutase, which is the principal antioxidant enzyme that neutralizes the toxic effects of reactive oxygen species. However, the direct cause for the increase in serum manganese is not understood and there is no direct correlation between serum manganese and hypothyroidism. Soldin and Aschner (2007) hypothesized that manganese may directly or indirectly affect the thyroid function by injuring the thyroid gland or dysregulating dopaminergic modulation of thyroid hormone synthesis.

More studies are needed to explain the real cause about the increase in serum manganese in hypothyroidism.

This work represents the first report about the increase in serum manganese in hypothyroidism patients. Furthermore, the overall results of this study suggest an abnormal metabolism of zinc, manganese, and selenium in hypothyroidism disease.

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